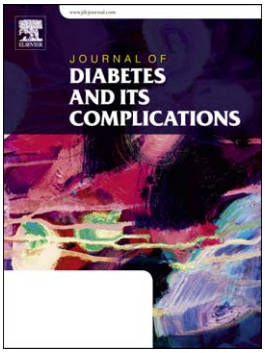

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PII: S1056-8727(16)30283-5
DOI: doi: 10.1016/j.jdiacomp.2016.07.004
Reference: JDC 6792

To appear in: *Journal of Diabetes and Its Complications*

Received date: 31 March 2016
Revised date: 8 July 2016
Accepted date: 9 July 2016

Please cite this article as: Dehghani, C., Russell, A.W., Perkins, B.A., Malik, R.A., Pritchard, N., Edwards, K., Shahidi, A.M., Srinivasan, S. & Efron, N., A rapid decline in corneal small fibres and occurrence of foot ulceration and Charcot foot, *Journal of Diabetes and Its Complications* (2016), doi: 10.1016/j.jdiacomp.2016.07.004

Case report

A rapid decline in corneal small fibres and occurrence of foot ulceration and Charcot foot

Cirous Dehghani[1], Anthony W. Russell[2,3], Bruce A. Perkins[4], Rayaz A. Malik[5,6], Nicola Pritchard[1], Katie Edwards[1], Ayda M. Shahidi[7], Sangeetha Srinivasan[1], and Nathan Efron[1]

[1]Institute of Health and Biomedical Innovation, Queensland University of Technology, Kelvin Grove, Queensland, Australia; [2]Princess Alexandra Hospital, Woolloongabba, Queensland, Australia; [3]School of Medicine, University of Queensland, Woolloongabba, Queensland, Australia; [4]Division of Endocrinology and Metabolism, Department of Medicine, University of Toronto, Toronto, Ontario, Canada; [5]Center for Endocrinology and Diabetes, Institute of Human Development, University of Manchester, Manchester, U.K; [6]Weill Cornell Medical College in Qatar, Doha, Qatar and [7]Annidis Corporation, Ottawa, Canada.

Correspondence to: Cirous Dehghani. Institute of Health and Biomedical Innovation, Queensland University of Technology, 60 Musk Avenue, Kelvin Grove, Queensland 4059, Australia. Email: c.dehghani@qut.edu.au. Tel.: +61 7 3138 6414.

Conflicts of interest: The authors report no conflicts of interest related to this article

Abstract

We present clinical, neuropathy and corneal nerve morphology data in a participant with type 2 diabetes who developed diabetic foot ulceration, partial amputation and Charcot during a longitudinal observational study. While conventional measures of neuropathy did not deteriorate significantly, corneal nerve parameters showed a rapid reduction prior to the development of foot complications.

Keywords: Diabetic peripheral neuropathy; corneal nerve morphology; diabetic foot complications

1. Introduction

Diabetic peripheral neuropathy (DPN), a common and chronic complication of diabetes, can lead to foot ulceration, Charcot foot and amputation with a significant impact on the quality of life of the patient and markedly increased health care costs [1,2]. These end points have been attributed primarily to a loss of protective sensation and large fibre neuropathy [3].

In vivo corneal confocal microscopy (IVCCM) [4] emerged more than a decade ago as a measure of small fibre neuropathy for DPN assessment [5] and has demonstrated considerable utility in early diagnosis [6], stratification of severity [7] and assessment of therapeutic efficacy [8,9] in DPN. This case report demonstrates that IVCCM identifies and tracks a rapid decline in small nerve fibres in relation to the development of diabetic foot ulceration and Charcot.

2. Case report

Data were collected prospectively over 7 years commencing from June 2009 from a 55 year old Caucasian male with type 2 diabetes (diagnosed in 2002) who was a participant in the LANDMark study [9]. The participant underwent examinations at baseline and at four subsequent visits and a final visit approximately 6.5 years from baseline. Annual assessments comprised of $HbA_{1c,}$ lipid profile and blood pressure and detailed evaluation of peripheral neuropathy including neuropathy disability

score (NDS), quantitative sensory testing (QST) of thermal and vibration perception, nerve conduction studies (NCS) and corneal nerve parameters measured using IVCCM. At baseline, no biochemistry and NCS were conducted for this participant, because these were not a part of the study protocol in 2009. Furthermore, no neuropathy assessment could be carried out (except IVCCM) at year-3 and final visits because of DPN complications of the affected right foot.

The following blood biochemistry parameters were recorded at year-1, year-2, year-3, year-4 and final year-6.5 visits: HbA1c – 7.5, 8.7, 9.3, 8.0 and 9.8 % (58, 72, 78, 64 and 84 mmol/mol); total cholesterol: 4.0, 5.1, 4.8, 3.0 and 5.2 mmol/L; HDL-cholesterol: 0.6, 0.9, 0.7, 0.7 and 0.7 mmol/L; LDL-cholesterol: 1.8, 2.9, 2.5. 1.0 and 3.3 mmol/L; Triglycerides: 3.4, 2.9, 3.4, 2.8 and 2.6 mmol/L (Figure 1a). Blood pressure was measured from baseline to final visit as follows: systolic: 123, 127, 109, 140, 119 and 115 mmHg; diastolic: 81, 80, 69, 82, 95 and 77 mmHg. The following neuropathy measures were recorded at baseline, year-1, year-2 and year-4 visits: NDS: 9, 10, 6 and 8; cold detection threshold: 20, 30, 28 and 30 °C; warm detection thresholds: 40, 34, 37 and 35 °C; vibration perception threshold: 8, 4, 6 and 7 Hz. In relation to NCS, no reproducible responses were elicited for the sural sensory nerve at any of the visits. Peroneal motor nerve conduction velocity (PMNCV, ankle to fibula head) was 34, 38 and 34 m/s for year-1, year-2 and year-4 visits. Figure 1b illustrates the trends over time in conventional measures of neuropathy.

The participant developed an ulcer on his right great toe 2.7 years after his baseline visit which healed after six months. In November 2012 (3.4 years after baseline) he underwent partial left great toe amputation secondary to a foot ulcer initiated 5 months prior to the amputation. The participant developed Charcot's foot (midfoot collapse) in November 2015 (approximately 6.5 years from baseline) and underwent IVCCM examination. IVCCM demonstrated a moderate to severe neuropathy at baseline followed by a rapid decline in corneal nerve fibre density (CNFD), nerve branch density (CNBD) and fibre length (CNFL) over the duration of the study (Figure 1c).

3. Discussion

Patients with diabetes may develop a spectrum of end stage complications as a consequence of DPN. There is a need for reliable methods to accurately discriminate those patients at higher risk of foot complications from those who are not. An abnormality in neurological examination, monofilament insensitivity and loss of vibration perception are traditionally deployed to identify patients at high risk of foot ulceration, whilst neurophysiology is advocated as the gold standard for identifying patients with DPN [3]. Alternative techniques such as IENFD and IVCCM assessment can also diagnose diabetic neuropathy [11] and help stratify the stage of neuropathy [7]. In relation to the case reported here we have compared the utility of a range of advocated measures of neuropathy, including IVCCM in relation to the development of both foot ulceration and Charcot foot.

Although with some notable variations, during the 6.5 years of observation the participant had poor glycaemic control and non-optimal lipid management evident by above optimal levels of LDL-cholesterol and triglycerides and suboptimal levels of HDL-cholesterol; however, the blood pressure control was acceptable. NDS showed variability but overall the patient had moderate to severe neuropathy. Thermal and vibration perception and PMNCV improved from baseline to the year-1 visit, but these measures at all remaining visits showed no deterioration, especially in relation to the occurrence of foot ulceration, amputation or the development of Charcot foot.

Notably, all corneal nerve parameters showed a reduction prior to the development of foot ulceration and partial amputation and also continued to decline before the development of Charcot's foot at the final visit. Over the 6.5 years of follow up, CNFD, CNBD and CNFL showed an annual rate of deterioration of 1.9 nerve/mm^2, 2.8 branch/mm^2 and 1.1 mm/mm^2, respectively. This reduction is much more marked than that observed in healthy control subjects in whom we have previously shown a linear decrease of 0.05 mm/mm^2 in CNFL per one year increase in age [12,13] and a reduction of 1 nerve/mm^2 (CNFD) per year with no change in CNBD and CNFL in individuals with type 1 diabetes [14].

Sensory small nerve fibres play an important role in the process of wound healing in diabetes [15]. This case report implies a potential value of IVCCM as compared to

QST and neurophysiology in identifying a dramatic loss of small nerve fibres and consequently predicting the future development of foot ulceration and Charcot. This technique may allow the identification of high risk individuals who may benefit from diabetic foot care programs and educational interventions, or who may enter clinical trials of interventions for the prevention of the development of the late sequelae of neuropathy. Future research should focus on the levels of longitudinal corneal nerve change that can discriminate those who are at risk of foot complications.

Acknowledgments

Funding was provided by the National Health and Medical Research Council of Australia (492730), the JDRFI (8-2008-362) and the NIH (DP3DK104386)

Figure Legends

Figure 1. Changes in (a) blood biochemistry parameters, (b) conventional measures of neuropathy and (c) corneal nerve parameters in this case over 6.5 years of follow-up and occurrence of foot complications. NDS: neuropathy disability score; CDT: cold detection threshold; WDT: warm detection threshold; VPT: vibration perception threshold; PMNCV: peroneal motor nerve conduction velocity; CNFD: corneal nerve fibre density; CNBD: corneal nerve branch density and CNFL: corneal nerve fibre length.

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Figure 1